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Risk factors for community-acquired pneumonia with influenza A/H1N1 in southern Israel☆

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SUMMARY

Objectives: To determine the risk factors for community-acquired pneumonia (CAP) with influenza A/H1N1 flu in our region.
Methods: Adult patients with CAP from July 2009 to February 2010 who were screened for influenza A/H1N1 were identified retrospectively. This was a retrospective case–control study. Cases had CAP with influenza A/H1N1 and controls had CAP without influenza A/H1N1. Patient files were reviewed for demographics, clinical characteristics, treatment, and outcome.
Results: Three hundred and eight patients with CAP were identified: 107 cases and 201 controls. For cases vs. controls there were significant differences in the following: median age (40 (range 18–82) vs. 56 (range 18–89) years; $p < 0.001$), female gender (63.6% vs. 44.3%; $p < 0.05$), Bedouin Arab origin (41.1% vs. 26.4%; $p < 0.05$), pyrexia (97.6% vs. 88.5%; $p < 0.01$), cough (96.3% vs. 75%; $p < 0.05$), admission to the intensive care unit (18.7% vs. 10.6%; $p < 0.05$), and CURB-65 score ≥ 3 (2.8% vs. 11.4%; $p < 0.05$). Laboratory values including white blood cell (WBC) and platelet counts were lower in cases than in controls, whereas creatine phosphokinase and lactate dehydrogenase levels were higher ($p < 0.01$). By logistic regression models, young age, Bedouin origin, and lower WBC and platelet counts were independent risk factors for the acquisition of CAP with influenza A/H1N1.
Conclusions: In our region CAP with influenza A/H1N1 occurred in younger females of Bedouin Arab origin with less co-morbidity. No difference in mortality was found. We believe that inequalities in socioeconomic conditions could explain our findings.

1. Introduction

April 2009 marked the beginning of the 2009 influenza A/H1N1 pandemic (2009 H1N1). It is estimated that approximately 43–89 million persons in the USA became ill with 2009 H1N1 between April 2009 and April 2010.[1] As at August 2010, more than 214 countries and overseas territories or communities had reported laboratory-confirmed cases of 2009 H1N1, including 18 449 deaths.[2] This flu can be associated with severe illness and death in young, previously healthy individuals. At least 5% of patients with confirmed 2009 H1N1 infections have been found to develop pneumonia.[3] Symptoms such as dyspnea, wheezing, vomiting, and diarrhea are associated with pneumonia resulting from pandemic H1N1 infection.[3] 2009 H1N1 pneumonia has been associated with prolonged hospital admission, increased intensive care unit (ICU) admission, and increased disability compared to non-pneumonia 2009 H1N1.[4] Severe community-acquired pneumonia (CAP) has been described among young adults with 2009 H1N1, attributed to delayed initiation of antiviral therapy.[5]

Well-known risk factors for the acquisition of 2009 H1N1 have been described, but risk factors for CAP with 2009 H1N1 are less known. Our aim was to determine the risk factors for CAP with influenza A/H1N1 flu in our region.

2. Materials and methods

2.1. Subjects

The study was performed at Soroka University Medical Center, a 1000-bed tertiary-care teaching hospital, serving more than 500 000 inhabitants in southern Israel. Our region can be characterized

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Table 1
Detection of respiratory viruses

Viral set		Primers and probe sequence	Concentration (nM)
H1N1 (Ref. 6)	H1-Ger SW-F	cat ttg aaa ggt ttg aga tat tcc c	400
	H1-Ger SW-R	atg ctg ccg tta cac ctt tgt	400
	H1-Ger SW-P	Cy-5-aca agt tca tgg ccc aat cat gac tcg-BBQ	200
Influenza A universal	Inf-A-F (CDC)	gac cra tcc tgt cac ctc tga c	300
	Inf-A-R (CDC)	agg gca tty tgg aca aak cgt cta	300
	Inf-A-P (CDC)	FAM-tgc agt cct cgc tca ctg ggc acg-BHQ	200

as consisting of urban areas, inhabited by a nearly all Jewish population with a minority of Bedouin Arabs, and a surrounding large arid Negev desert area where a nomad population of mostly Bedouin Arabs live. We retrospectively identified all adults who presented to our emergency room with influenza-like illness (ILI) and who were screened for influenza A/H1N1 during the study period of July 2009 through February 2010, from the records of the Virology Laboratory. We then divided these hospitalized patients with pneumonia into cases and controls. Cases were defined as any patient aged ≥18 years hospitalized with pneumonia who tested positive for influenza A/H1N1. Controls were defined as any patient aged ≥18 years hospitalized with pneumonia who tested negative for influenza A/H1N1.

2.2. Measures

Data were collected using a pre-designed structured questionnaire covering demographic background including age, gender, origin, ward in which they were hospitalized, pregnancy, smoking, body mass index (BMI), CURB-65 score, Charlson co-morbidity index, and underlying diseases. The CURB-65 criteria were dichotomized into high (≥3, indicating higher risk of death) and low (≤2, indicating lower risk of death). The presence of symptoms of respiratory infection (ILI) and gastrointestinal complaints, as well as relevant laboratory data such as complete blood count, renal function tests, liver enzymes, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), blood gases, and sputum and blood cultures were noted. Chest X-ray results, antiviral and antibiotic treatment, length of in-hospital stay, end of hospitalization, and 30-day mortality were also recorded.

2.3. Sampling

All patients presenting to our emergency room with ILI were tested for influenza A/H1N1. The samples were taken as close as possible to the time of hospital admission and in no case more than 24 h later. Three consecutive samples were taken from each participant: one oropharyngeal swab and two nasopharyngeal swabs, using swab applicators (Virocult Sigma 3, Medical Wire & Equipment, UK).

After sampling, the nasopharyngeal and oropharyngeal swab applicators were cut and placed together in one tube containing 3.0 ml of RPMI solution (Biological Industries, Beit Haaemek, Israel). The test tube with the swabs was vortexed for 5 min, after which the head of the applicator was drained against the sides of the test tubes and then removed. Nucleic acid extraction was performed using NucliSENS easyMAG (bioMérieux, Marcy l'Etoile, France), according to the manufacturer's instructions. A quantity of 400 μl was extracted into 50 μl of elution solution.

2.4. Detection of respiratory viruses

Each sample was tested in parallel in one test tube for the following viruses: influenza A and influenza A H1N1. The sets of primers and probes used to detect the two viruses by multiplex hydrolysis probes-based real-time polymerase chain reaction (mqRT-PCR) are shown in Table 1.[6]

2.5. Pneumonia

CAP was diagnosed based on clinical features and a chest X-ray. All chest X-rays were reviewed by a radiologist who confirmed the diagnosis.

2.6. Statistical analysis

The sample size (confidence interval 95%, power 80%) was calculated using Epi Info version 4.3.4 software (CDC, Atlanta, GA, USA). For categorical variables, proportions were compared using Fisher's exact test or the Chi-square test, as appropriate. Continuous variables were analyzed with the Student's *t*-test or the Wilcoxon rank sum test, depending on the validity of the normality assumption. A two-tailed *p*-value of < 0.05 was considered significant. Multivariate analysis was performed using logistic regression. A significance level of <0.05 was used in this test. All analyses were performed using SPSS version 15 (IBM SPSS, Chicago, IL, USA).

3. Results

Three hundred and eight patients with CAP were identified: 107 cases and 201 controls. Cases were significantly younger, of female gender, and of Bedouin Arab origin (Table 2) than controls.

On the other hand, controls had a significantly higher rate of co-morbidities compared to cases, including smoking, diabetes,

Table 2
Demographic characteristics of the patient population, cases vs. controls

Variable	Cases ($n = 107$)	Controls ($n = 201$)	*p*-Value, OR (95% CI)
Age (median)	40 (18–82)	56 (18–89)	<0.001
Female gender	68 (63.6%)	89 (44.3%)	0.002, 2.19 (1.35–3.5)
Origin			
Bedouin Arab	44 (41.1%)	53 (26.4%)	0.008, 1.95 (1.18–3.2)
Residence			0.72
Home	105 (98.1%)	194 (96.5%)	
Nursing-home	2 (1.9%)	7 (3.5%)	
Smoker	19 (17.8%)	64 (33.7%)	0.011, 0.46 (0.24–0.76)

OR, odds ratio; CI, confidence interval.

Table 3
Underlying diseases, cases vs. controls

Variable	Cases (n = 107)	Controls (n = 201)	p-Value (95% CI)
Pregnancy	15/68 (22.1%)	7/89 (7.9%)	0.01 (1.17–9.7)
Peripartum	5/68 (7.4%)	6/89 (6.7%)	0.747
Obesity	31 (29.0%)	41 (22.5%)	0.26
Chronic lung disease	20 (18.7%)	45 (22.4%)	0.27
Diabetes	17 (15.9%)	53 (26.4%)	0.045 (0.29–0.967)
Cardiovascular diseases	2 (1.9%)	38 (18.9%)	<0.001 (0.02–0.35)
Congestive heart failure	6 (5.6%)	28 (13.9%)	0.034 (0.15–0.91)
Chronic renal failure[a]	4 (3.7%)	22 (10.9%)	0.032 (0.106–0.94)
Peripheral vascular disease	1 (0.9%)	5 (2.5%)	0.68
CVA/TIA	5 (4.7%)	14 (7.0%)	0.62
Liver disease	4 (3.7%)	4 (2.0%)	0.45
Malignancy	10 (9.3%)	23 (11.4%)	0.57
Organic brain syndrome	6 (5.6%)	27 (13.4%)	0.03 (0.17–0.92)

CI, confidence interval; CVA, cerebrovascular accident; TIA, transient ischemic attack.
[a] Creatinine >2 mg/dl.

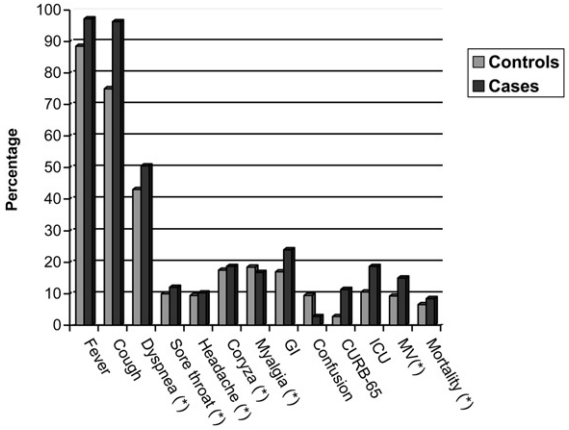

Figure 1. Clinical characteristics of patients with CAP (*p-value = non-significant; GI = gastrointestinal symptoms; ICU = admissions to the intensive care unit; MV = mechanical ventilation).

organic brain syndrome, congestive heart failure, chronic renal failure, and cardiovascular disease (Table 3). Chronic lung disease, obesity, and the pregnancy rate were similar in both groups (p = not significant).

Patient clinical characteristics at hospital admission are presented in Figure 1. Among the cases there was a greater proportion of patients with pyrexia (>38 °C) (odds ratio (OR) 4.5, 95% confidence interval (CI) 1.32–15.37, p = 0.006), cough (OR 8.58, 95% CI 3.0–24.5, $p < 0.0001$), and CURB-65 score of ≤2 (OR 4.48, 95% CI 1.24–19.22, p = 0.017).

Table 4 summarizes the laboratory findings. In cases vs. controls, laboratory values including white blood cell (WBC), polymorphonuclear neutrophil (PMN) and platelet counts, and urea and creatinine levels were lower, whereas CPK and LDH levels were significantly higher ($p < 0.01$). Bacteremia was found in 9.9% of controls vs. 1.1% of cases ($p < 0.01$). Chest X-rays showing unilateral infiltrates were the most frequent finding: 79% in cases vs. 71% in controls (p = not significant).

Prompt antibiotic treatment was initiated for all cases and controls and antiviral treatment (oseltamivir) was initiated in all cases. With regard to ICU admission, 18.7% of cases were admitted to the ICU vs. 10.6% of the control group ($p < 0.05$). The number of patients requiring mechanical ventilation was 15% vs. 9.3%, the mean length of hospitalization was 4 days (range 1–45) vs. 3 days (range 1–55), and the in-hospital crude mortality rate was 8.5% vs. 6.6%, in the case and control groups, respectively (all p = not significant).

Table 4
Laboratory values, cases vs. controls

Variable	Cases	Controls	p-Value
Hemoglobin g/dl, mean (± SD)	12.4 ± 1.9	12.9 ± 7.5	0.471
WBC × 10^9/l, mean (± SD)	8.703 ± 6.499	11.791 ± 6.821	<0.001
PMN × 10^9/l, mean (± SD)	6.958 ± 5.453	9.881 ± 7.472	<0.001
Lymphocytes × 10^9/l, mean (± SD)	1.312 ± 2.027	1.348 ± 0.988	0.833
PLT × 10^9/l, mean (± SD)	202.514 ± 92.231	248.170 ± 106.427	<0.001
Glucose mg/dl, median (range)	109 (40–525)	117 (69–563)	0.553
Urea mg/dl, median (range)	27 (5–190)	33 (7–225)	<0.001
Creatinine mg/dl, median (range)	0.73 (0.2–7.3)	0.87 (0.1–13.5)	0.026
Sodium mEq/l, median (range)	136 (120–143)	136.5 (124–159)	0.128
CPK U/l, median (range)	120 (26–7346)	70 (9–3166)	0.003
LDH U/l, median (range)	558 (323–1951)	496 (205-2270)	0.006
SGPT U/l, median (range)	22 (7–245)	22 (4–881)	0.513
SGOT U/l, median (range)	29 (9–306)	27 (8–129)	0.989
Positive blood cultures,[a] n (%)	1 (1.1%)	14 (9.9%)	0.004
Positive sputum cultures,[b] n (%)	0 (0%)	23 (67.6%)	<0.001

SD, standard deviation; WBC, white blood cells; PMN, polymorphonuclear neutrophils; PLT, platelets; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase.
[a] Blood cultures in cases were positive for: *Escherichia coli* (1); blood cultures in controls were positive for: coagulase-negative Staphylococcus (8), *Streptococcus pneumoniae* (3), *Escherichia coli* (1), *Propionibacterium granulosum* (1), Micrococcus (1).
[b] Sputum cultures in controls (some grew more than one pathogen) were positive for: *Candida albicans* (10), non-albicans Candida (6), *Aspergillus flavus* (1), *Streptococcus pneumoniae* (2), group B Streptococcus (1), *Enterococcus spp* (1), methicillin-sensitive *Staphylococcus aureus* (2), methicillin-resistant *Staphylococcus aureus* (1), coagulase-negative Staphylococcus (1), *Haemophilus influenzae* (3), *Pseudomonas aeruginosa* (7), *Stenotrophomonas maltophilia* (3), *Enterobacter spp* (3), *Klebsiella spp* (2).

By logistic regression models, young age (95% CI 1.077–1.806), Bedouin origin (95% CI 1.031–8.615), and lower WBC (95% CI 1.32–1.980) and platelet (95% CI 1.103–1.980) counts were independent risk factors for CAP with influenza A/H1N1.

4. Discussion

Pneumonia has been found in 5–29% of adult patients hospitalized with laboratory-confirmed 2009 influenza A/H1N1, and in up to 40% in a mixed cohort of pediatric and adult patients.[3,7–9]

Clinical features independently associated with pneumonia in patients with this pandemic flu include dyspnea, wheezing, vomiting, and diarrhea.[3] Studies have further shown that antiviral therapy started at >48 h after the onset of symptoms tends to be more common in patients with pneumonia or other influenza complications than in those without.[3,10]

Nguyen-Van-Tam et al. described risk factors for a severe outcome in patients hospitalized with pandemic influenza A/H1N1; an abnormal chest X-ray or a raised C-reactive protein level, especially in patients recorded as obese or in those with pulmonary conditions other than asthma or chronic obstructive pulmonary disease, indicated a potentially serious outcome.[7] Mulrennan et al. concluded that the CURB-65 score does not predict severe 2009 pandemic influenza A/H1N1 CAP or the need for ICU admission.[4]

Non-specific laboratory tests have been researched as indicators of severity of pandemic H1N1 with pneumonia. Cunha et al. showed that while the presence of otherwise unexplained relative lymphopenia and thrombocytopenia were key diagnostic markers for hospitalized adults with pandemic influenza A/H1N1 pneumonia, their degree and duration did not predict clinical severity. They also noted an elevated CPK level, which likewise was not found to predict clinical severity or adverse outcomes.[11]

In our patient population, we found young age, Bedouin Arab origin, and lower WBC and platelet counts to be independent risk factors for the acquisition of CAP with influenza A/H1N1.

A higher incidence of CAP hospitalizations has previously been found in adult Bedouin Arabs compared to the adult Jewish population in southern Israel, although no difference was demonstrated in the clinical outcomes.[12] In comparison, Bedouin Arab children have been shown to be at a higher risk of hospitalization for infectious diseases (diarrhea and pneumonia) in early childhood as compared to Jewish children.[13] In Bedouin Arab children with CAP, a more severe clinical course and a higher rate of morbidity than in Jewish children has been demonstrated.[14] Different socioeconomic factors (e.g., a very high birth rate, crowded living conditions, low income) could explain the higher rate of CAP in Bedouin Arabs living in southern Israel. 2009 H1N1 has been investigated in ethnic minority groups worldwide, showing higher attack rates and a worse prognosis in these populations. The first wave of the 2009 H1N1 pandemic in Wisconsin USA disproportionately affected hospitalized patients who were African Americans, Asians, and Hispanics compared to non-Hispanic whites.[15] Indigenous populations from Australia, Canada, and New Zealand have been found to have a three to six times higher rate of hospitalization and death associated with infection with the 2009 H1N1 virus.[16] In England, mortality rates were found to be higher for Bangladeshi and Pakistani children than for white British children.[17]

Previous studies have reported 7–14.7% mortality in patients with pneumonia and influenza A/H1N1.[18,19] Independent risk factors for death are progressive dyspnea after resolution of fever and a higher APACHE II (acute physiology and chronic health evaluation) score on presentation.[18] Cui et al. found an association between obesity and lymphopenia that was not restored after 5 days of treatment, and a poor outcome in hospitalized pneumonia patients with 2009 pandemic H1N1.[19] The outcome of our CAP patients, cases and controls, was similar, with 8.5% and 6.6% mortality, respectively (p = not significant). Possible explanations for the relatively favorable clinical outcome in our patients include: patients of a young age, low co-morbidity rate, accessible rapid diagnostic tests (RT-PCR), and early administration of oseltamivir and antibiotic treatment. In comparison to other studies, we included only patients presenting with CAP, excluding patients with hospital-acquired pneumonia; this might further contribute to our findings. However, our study design did not aim to calculate the poor outcome or attributable mortality of CAP with A/H1N1 in our institution.

We conclude that in our region, the acquisition of CAP with influenza A/H1N1 occurred in patients of Bedouin Arab origin, who were younger females with fewer co-morbid conditions. We believe that this and other similar 'high-risk' populations worldwide must be targeted in particular by an intensive and strict mass influenza vaccination effort.

Ethical approval: The work was approved by the institutional Helsinki committee.

Conflict of interest: No competing interest declared.

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